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THE UNIVERSITY OF TORONTO MEDICAL JOURNAL

(An Undergraduate Publication)

This journal is published seven times a year, November to May, by the Medical Society of the University of Toronto, to serve as a medium for student expression and to bring to the student recent articles of scientific interest.

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Volume XII

TORONTO, FEBRUARY, 1935

Number 4

EDITORIAL

ARTS AND MEDICINE.

During recent years, the abolition of the course in the Biological and Medical Sciences has often been suggested. Those who favour this move feel that the B. and M. course has wandered too far from its original purpose of giving a broader general training in the "arts" than is provided by the "straight" medical course. Others have suggested that an attempt be made to revise the curriculum of the course so that it will once more fulfil its original purpose. In the better medical schools in the United States, where educational problems are essentially similar to our own, there is a growing tendency to shorten the medi-

cal course and to make pre-medical arts training compulsory. The feeling is that the student who has a thorough pre-medical training of a general nature does better than the one who has more definitely scientific training before entering clinical medicine. In reporting a study of the examination results of first and second year medical students in the United States, F. C. Zapffe says: "On the whole, then, one is tempted to say emphatically that the best preparation for the study of medicine is the pursuit of studies leading to the A. B. degree; more culture; less science." If the Toronto Medical School is ultimately going to demand some pre-medical training in arts as an

entrance requirement, it would seem wise to retain the B. and M. Course and to use it in experiments directed toward finding out the type of pre-medical education best suited to Canadian needs.

Judging from the experience quoted above, such a pre-medical course should entirely exclude definitely medical subjects. It would probably include a thorough grounding in biology, using the term in its broadest sense, and including comparative anatomy and experimental biology. The basic sciences, such as mathematics and physics, could be taught with the emphasis on general principles rather than on technical details. Chemistry courses should emphasize organic and colloidal chemistry, which is the basis of the study of life rather than inorganic and analytical chemistry. An attempt should be made to correlate this scientific knowledge with life, and to broaden the interests of the student, by a study of the "humanities." History, in a wide sense, including the history of the evolution of art, music, government and particularly science, would be of great value. The study of literature would be one of the most important parts of the course if it left the student with a taste for good books and a desire to read. Too often, the courses offered to the science student leave him with a horror of Shakespeare's works, and nothing more. The rudiments of philosophy and the principles of logic, with special reference to the development of the scientific method, would be an aid in unifying the whole course. In the last year of the four-year arts course general biochemistry and physiology could

be introduced, but the more purely medical aspects of these subjects and the whole of human anatomy should be left for the first year of the subsequent four-year medical course. Such an Arts course would be an excellent training for clinical medicine, but would probably not provide a suitable preparation for research in the medical sciences. Research demands a more intensive training in the basic sciences than could be given in this course.

The medical course at the University of Toronto is, at present, second to none. However, it cannot remain static and retain this pre-eminence. Changes will undoubtedly have to be made in the curriculum to keep pace with the changing demands which will be made upon the students after graduation. If the change is to be in the direction of pre-medical training, as the experience in the United States suggests, the B. and M. course seems to offer an excellent means for testing the idea that a broader and less technical pre-medical training results in better medical students in the clinical years than does the present highly specialized pre-medical curriculum.

It is hoped that this editorial will arouse some discussion among the students, concerning this problem. If the students were more keenly aware of the problems of medical education they would, not only more deeply appreciate the excellent course which is given them at present, but might also be able to offer some constructive criticism which would aid in the continuous improvement of the course to keep pace with changing needs.



OVARIAN HORMONES

By A. L. CHUTE, M.A., '36.

At first glance it would appear that the ovary should be the prime regulator in the control of sexual functions but we know that while it is responsible for the production of the essential germ cell of the female yet these cannot develop in the absence of the secretion from the anterior pituitary. On the other hand we also know that the ovary exerts a profound influence on the activity of the pituitary. It is therefore like trying to find the head of the snake that swallowed its tail to determine which is the prime factor.

Site of Production of Oestrin.

If we examine the ovary closely, there would appear to be three main structures which might be responsible for endocrine production.

1. The interstitial tissue
2. The cells of the Graafian follicle
3. The cells of the corpus luteum.

That the interstitial tissue was a possible source of hormone production and that it might temporarily be an accessory source of oestrin, in certain conditions where the follicles have been inhibited, has been shown by some investigators. Following the demonstration that X-radiation destroyed embryonic cells in tissues, this experimental procedure was tried on mammalian ovaries. In earlier work, the majority of investigators reported either permanent or temporary sterilization by destruction of the ova. In many cases this was followed by a distinct decline and disappearance of the sexual characteristics dependent upon normal endocrine function. More recently, Parks Brambell and Fielding, and others, have shown that with carefully graded doses of X-rays it is possible to destroy the ova in the mouse ovary with-

out apparently influencing the endocrine function. When immature animals were subjected to critical doses, the follicles and ova were destroyed and new growths of epithelioid tissue from the dermal epithelium occurred. These were quite similar to ovogenetic growths during embryonic life except that they contained no ova. In adults, ova were destroyed and remnants of follicles left in more or less disorganized condition to constitute the major portion of the ovary. In both cases, however, ovarian hormonal function was maintained, as judged by the fact that they were capable of inducing cyclic growth changes in the genital tract which are characteristic of the normal cycle in mature animals. Nevertheless it must be pointed out that species differences are marked and larger animals fail to give similar results. Whether or not the tissue responsible for this endocrine activity of X-rayed ovaries is strictly comparable to the interstitial tissue which is found in the normal ovary is still to be determined.

Experiments on mice, however, are clear cut and indicate that disorganized follicular tissue or some new growth which formerly had the potentialities for follicular organization, may be capable of carrying on the secretion of oestrin. This evidence is not proof, however, that normally the maturing follicle does not serve this function. In fact it has been abundantly proven that the developing Graafian follicle is a major seat for the production of the primary female sex hormone.

Properties and Action of Oestrin.

Before proceeding with a discussion of this primary female sex hormone, it probably would not be out of place to enumerate some of the various

names which have been used by different investigators to designate this substance. Thus it has been called—Theelin, folliculin, oestrin, progynon, menformon, and thelykinin. Though many of the effects of ovarian extracts had been studied previously, it was not till 1929 that an active crystalline preparation was found. Doisy and others recovered such a substance from pregnancy urine. It had a chemical formula of $C_{18}H_{22}O_2$. The next year Marrian produced a similar though not an identical substance $C_{18}H_{24}O_3$. The first substance is called Theelin and the second Theelol by the Americans. But as Marrian points out Oestrin would appear to be a better name, as it indicates the action of the substance, that is, to produce oestrus.

The first, because of its chemical nature, he calls ketohydroxy-oestrin and the other he calls trihydroxy-oestrin. Biological assay has shown that the ketohydroxy form is three to five times as potent as the trihydroxy form. Recently Hildebrandt, by hydrogenation of the ketohydroxy form, has produced a substance with many more times the potency of either of the others. If the substance, dhydro-oestrin thus formed, is still further hydrogenated, it takes on the properties of the male sex hormone, but this does not concern us here. Oestrus producing substances have been demonstrated in a wide variety of mammalian and plant tissues and even in unicellular organisms. It is conceivable that a number of compounds may produce the oestrus response but thus far the ones mentioned are the only ones which have been isolated. Concerning the fate of oestrin; Zondek has published a recent report in which he injected enormous doses of oestrin into mice. In 24 hours less than 1% was recoverable from the whole animal. However by a method of hydrolysis he was able to recover 20% which had been apparently partially fixed or destroyed, but only 6% could be recovered at the end of 48 hours. This all occurred before

any change in the genital organs could be appreciated. His experiments led him to believe that the liver and its enzymes were largely responsible for its inactivation.

Before describing the action of oestrin on the genital tract it probably would be of advantage to discuss the condition of heat or oestrus in an animal such as the rat, in comparison with menstruation in the primates, such as the great apes or man. It was the inability of the earlier workers to recognize the similarity and the differences in these two conditions which gave rise to many difficulties. In the rat, periods of oestrus occur every 3-4 days in the absence of pregnancy. The early changes consist in a vascular engorgement of uterus tubes and vagina. The endometrium shows a marked proliferation with many mitotic figures and finally a secretion is produced which distends the uterus. The vaginal epithelium which was formerly thin is now greatly thickened. The lumen, which in the resting state, shows large numbers of polymorphonuclear cells when a smear of its contents is made, now shows no such cells but the large desquamated cells of the cornified epithelium. This reaction is so sharp and distinctive that it has been used as a method of assay for oestrin. If now the cervix is stimulated mechanically, or mating takes place with a vasectomised male, a further development of the endometrium occurs and forms a so-called deciduoma or pseudo-pregnancy. Finally this breaks down, is discharged, and the genital tract returns to the resting stage.

In man there is likewise a hyperaemia and then a hyperplasia of the endometrium from the 5th to the 14-16 day after the last menstruation. At this time the glands are straight and show little evidence of secretion. After ovulation, which occurs at this time, a further growth of the endometrium, similar to that obtained on stimulating the cervix of the rat, is produced. The glands become tortuous

and begin to secrete. Finally, about the 28th day, the whole process breaks down and menstruation sets in.

It would be impossible in a paper of this length to describe the various experiments which have led to the explanation of these phenomena and I shall therefore content myself with relating the generally accepted views on the subject. Under the influence of prolactin A from the ant. pituitary, the ovary is stimulated to folliculization. This, as already stated, means an increase in oestrin production.

Briefly the effects of oestrin are as follows: Oestrin, like adrenaline, probably acts, in part at least, by producing a local effect on the blood vessels. This explains the vascular engorgement and also probably accounts for the increased growth, though this may be due in part to the direct action of oestrin on the cells of the genital tract. Oestrin alone can produce all the changes described in the rat except those following the stimulation of the cervix, i.e., the pseudopregnancy reaction. Similarly in the monkey and presumably in man, oestrin alone can produce all the changes observed up to the 14-16 day of the cycle when ovulation occurs. The difference between the rat and the primate is that, in the former, the corpus luteum phase is very short and oestrus changes are due almost entirely to oestrin, while in the primates the corpus luteum carries on from the point of ovulation. A similar condition can be produced in the rat by stimulating the cervix which prolongs the life of the corpus luteum and produces a picture comparable to the full menstrual cycle in the primate.

The cause of menstruation is thought to be due to a lack of oestrin. Thus it has been shown that at any time in the cycle, if oestrin is removed, the genitalia revert to the resting condition. The question then arises why does menstruation not occur on the 16th day in the primate. The solution lies in the fact that recently the corpus luteum has been shown to produce

oestrin as well as its own proper hormone, at least for a limited time. Oestrin also affects the musculature of the uterus. Both in vivo and in vitro it produces a slower but more powerful contraction of the uterine muscle and increases its oxygen requirement.

Besides its effect on the genitalia, oestrin also acts on the breasts. It is the onset of ovarian function at puberty that leads to a growth of these organs. In a general way it may be said that oestrin causes a growth of the duct tissue, while the hormone of the corpus luteum causes an increase in growth of the secreting elements of the gland.

As to the function of oestrin during pregnancy, little is known, though many theories have been advanced. It no doubt promotes further growth of the mammae and also acts as a check to the action of prolactin of the anterior pituitary (Collip & Riddell). It has also been suggested that the presence of large amounts of oestrin are responsible for the amenorrhoea of pregnancy, since it is the lack of this substance which in the non-pregnant individual brings on the monthly flow. In this regard, however, it must be stated that oestrin is found only in certain species during pregnancy. That the large amounts of oestrin found at term may, by increasing uterine contraction, bring on labour has also been suggested. Furthermore it has been demonstrated that oestrin definitely sensitises the uterus to the action of oxytocin from the posterior pituitary. The source of the oestrin during pregnancy is in doubt. Folliculization is suspended but the corpus luteum is known to produce this for the first third of pregnancy and castration experiments lead one to believe that large amounts are also formed by the placenta.

Corpus Luteum.

Turning now to the corpus luteum, we find that at least two hormones have been isolated from this body. One, like oestrin, has a multitude of names,

being called corpus luteum hormone, corporin, progestin, beta-factor, and lutin; and the other is called relaxin. Corporin has recently been isolated by Butenandt. Some of the actions of this hormone have already been touched on but there is one point which should be emphasized here, which is, neither corporin or relaxin have any effect in the body unless the tissues upon which these hormones act have been previously under the influence of oestrin. Whether the corpus luteum can be developed only through the action of prolan B, or whether it is merely a natural sequence of folliculization is still a matter of doubt. Most of the evidence would seem to favour the necessity for prolan B.

The functions of corporin are varied. It is known to inhibit ovulation for, if the corpus luteum is removed, the next ovulation is accelerated (Loeb). It has long been thought to be indispensable for the maintenance of pregnancy. This is true for some species but in man at least, total extirpation of the ovaries during pregnancy does not necessarily or even usually terminate gestation. However, it has been well established that the corpus luteum is responsible for the building up of the endometrium from ovulation to the pre-gestational stage and favours implantation and fixation of the embryo. It also exerts a direct effect on uterine muscle which is antagonistic to that of oestrin. Namely it causes a lessening and slowing of uterine contractions, thereby still further enhancing the opportunity for the ovum to implant itself. Its power of stimulating the growth of the glandular elements of the breast has already been mentioned.

Various factors have been discovered which affect the life of the corpus luteum. Most important of these is the effect of pregnancy. It is also prolonged by pseudopregnancy. In lactation it has been shown that persistence of the corpus luteum varies directly with the volume of milk produced.

Hysterectomy in the guinea pig also prolongs the life of this structure. What the significance of these findings is, is not quite clear but experiments have shown that, though the life of the corpus luteum may be prolonged, its physiological activity may not be.

I shall only say a word concerning relaxin. It is found in most species except the cow and man. It produces its most profound effects in the guinea pig and pocket gopher. In these it produces great relaxation of the pelvic ligaments and in the gopher leads even to resorption of bone. The amazing thing is that if male members of these animals are given a preliminary course of oestrin, they too show all these effects if relaxin is administered.

Uterine Reflexes.

Leaving for a moment the strictly hormonal side of the picture, a brief consideration of the influence of the uterus upon these mechanisms would seem to be in order. In most instances uterine effects would seem to be in the nature of reflexes, the afferent arc of which is nervous, activating the anterior pituitary, the efferent arc being hormonal from the pituitary, acting directly or through the ovary. The first condition to which we shall call attention is the production of pseudo-pregnancy in the rat or rabbit following irritation of the uterine cervix. It has been suggested that some such factor in man may be responsible for the prevention of the ensuing menstruation following pregnancy for, though not impossible, it would seem highly improbable that so small an organism as the early ovum could produce sufficient hormone, or X-factor to maintain the status quo while it developed to such a stage that it could do this. On the other hand, a reflex stimulation of the pituitary and through it of the ovary, has been definitely proved in the case of the rabbit. Another interesting observation is the onset of the climacteric at varying intervals after hysterectomy but in most cases

definitely earlier than in normal individuals. Finally, Collip showed recently that if the uterus of a guinea pig were emptied by caesarian section, lactation promptly set in. However if the uterus were filled with paraffin lactation was prevented. This he interprets as a reflex inhibition of the prolactin of the anterior pituitary.

Clinical Applications.

A paper on ovarian hormones would scarcely be complete without some reference to their use as therapeutic agents. The most outstanding success to far has been that of Kaufmann of Berlin. He has been able to produce true menstruation, as judged by histological examination of curettings, in a woman whose ovaries had been removed five years previously. To do this he was compelled to use a million international units of oestrin over a preliminary period followed by the use of ninety rabbit units of corporin. The most valuable part of this experiment is that it serves to point out how hopelessly inadequate former dosages had been. Parks, from his work on monkeys, had predicted earlier that there was a direct relationship between body weight and the dosage required. It is fortunate therefore that more potent products like dihydro-oestrin are being prepared.

Experiments such as these are of value, when well controlled, but nu-

merous reports have appeared on the use of endocrine extracts for a wide variety of conditions. They have been used in some instances for sterility and others for contraception. They have been given to prevent miscarriage or to induce abortion. They have been employed for hypogenitalism, dysmenorrhoea, dyspareunia, frigidity, pernicious vomiting of pregnancy and climacteric symptoms. They have also been used for haemophilia, hypertension, endocrinopathies, dermatoses, psychopathies, and many other conditions.

The pharmaceutical manufacturers, as might be expected, are unrestrained in their enthusiasm. They cite indications and dosage with an authoritative-ness unjustified by our present knowledge. In the experience of trusted workers, results have for the most part, been disappointing. Carefully controlled observations of the action of these substances in human beings are scanty. Effects of possibly harmful nature have been noted so that a warning must be given against their indiscriminate use.

It must be remembered, however, that the field has only recently been sown and the harvest must not be expected too soon. In future, when indications are clearer and preparations more potent, we may expect results as striking as are now obtained with thyroid or insulin.

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THE SEX HORMONES OF THE PITUITARY GLAND

By O. M. SOLANDT, M.A., B.Sc. (Med.), '36.

In most species of mammals, there is some sort of cyclic change associated with the sexual functions of the female. In lower animals this takes the form of regularly recurring periods of 'heat', the so-called oestrus cycle. In man and the other primates, menstruation is the chief outward manifestation of this cyclic activity. It has long been known, especially in the case of the common laboratory animals, that these changes are associated with synchronous changes in the ovaries. Further investigation suggested that these rhythmic changes in the ovary were brought about by some extrinsic factor acting upon the ovary. In recent years it has been conclusively proven that secretions of the anterior lobe of the pituitary gland control these ovarian changes.

The dependence of the ovary upon the pituitary gland was first conclusively shown by hypophysectomy. Following this operation, all sexual activity ceases and there is atrophy of the ovaries or testes and cessation of development of the accessory reproductive organs. This pituitary-gonad relationship is reciprocal since castration results in characteristic histological and secretory changes in the pituitary. This demonstration of the dependence of the ovary upon the pituitary has led to a vast amount of research in an attempt to isolate the active factor or factors in the pituitary and to elucidate their mode of action upon the ovary. It is impossible to treat all this work in chronological order so an attempt will be made to present merely a general view of the results to date.

Gonadotropic Hormones.

It is now fairly well established that the anterior lobe of the pituitary gland contains and secretes two gona-

dotropic hormones, a third hormone which is related in function to these and a separate lactogenic hormone. These are the hormones of the anterior pituitary which are directly concerned with reproduction. It is certain that some of the other hormones of the anterior pituitary are indirectly involved in the control of the reproductive processes but this relationship cannot be considered here. The two gonad stimulating hormones are variously known as prolan A and B, rho 1 and 2, and APH.A and APH.B. To avoid confusion with the similar, but not identical, substances found in the urine of pregnant women, apes and horses and known as prolan A and B, the anterior pituitary gonadotropic hormones will be referred to as APH.A and APH.B or collectively as the gonadotropic hormones of the anterior pituitary.

APH.A has been shown to cause maturation of the Graafian follicles in the ovary and the secretion of oestrin. That these two actions are not identical, is indicated by the fact that oestrin secretion can be induced even after all the follicles have been destroyed by irradiation with X-rays.

APH.B induces the formation of lutein tissues in the theca granulosa of the mature follicle. This luteinization can take place only after the follicle has been matured by the action of APH.A. There is, as yet, no evidence that the stimulation of secretion of the corpus luteum hormone is a specific function of APH.B but such secretion always follows the formation of the corpus luteum.

It is probable that these two hormones cooperate to bring about ovulation. APH.A alone produces a mature follicle but does not cause ovulation. APH.B alone causes excessive luteini-

zation with imprisonment of the ovum and the formation of corpora lutea atretica, except in immature animals where it is said to be without action. A proper combination of these two hormones results in the normal sequence of maturation, ovulation and luteinization. There is, as yet, no definite evidence that ovulation is not due to a specific substance which is contained in the luteinizing fraction and such a possibility has been suggested.

The two hormones APH.A and APH.B are probably secreted by the basophilic cells of the anterior pituitary since these cells alone are altered in various conditions in which the hormone output is modified.

Much of the recent interest in the sex hormones has centred about the Ascheim-Zondek test for pregnancy. This test depends on the presence, in the urine of pregnant women, of increased amounts of two hormones, prol-an A and prol-an B, having properties very similar to those outlined for APH.A and APH.B. Indeed, for many years, the two pairs of hormones were regarded as identical. Recent work has shown fairly conclusively that the gonadotropic hormones of pregnancy urine are not identical with those of the anterior pituitary. This evidence includes differences in the action of the two substances in many species of animals. The difference which is of greatest interest clinically, is the difference in the effect on the Rhesus monkey. Engle has shown that prol-an from pregnancy urine, which causes a complete follicular response in rodents, causes involution of the follicles and immediate cessation of oestrin secretion in the monkey. This is associated with cytolysis of the granulosa and slight luteinization of the theca interna. On the contrary, anterior pituitary gonadotropic hormones cause development of the follicles and luteinization of the granulosa. By combining the two, normal corpora lutea can be formed.

The fact that the ovarian changes

produced by pregnancy urine in rodents, can only be brought about by massive doses after hypophysectomy, whereas the amount of the anterior pituitary hormones required to produce the same effect is unchanged, not only emphasizes the difference between the hormones from the two sources but also has led to the discovery of what appears to be a third specific sex hormone in the anterior pituitary. Following the discovery that hypophysectomy rendered the ovaries of rats very insensitive to prol-an, attempts were made to combine the effects of prol-an and pituitary extracts. It was found that some factor in the pituitary extracts combined with the prol-an to make it a seffective in the pituitary-less animal as in the normal, and to increase its effect in the normal immature animal. This factor has been called the synergist or activator of the pituitary. Evans has prepared it free from thyreotropic, lactogenic and growth hormones and with only traces of gonadotropic activity. He has also demonstrated its specific action on the semeniferous tubules of the rat's testis. In view of these facts he believes that it is distinct from all the known hormones of the anterior pituitary.

The Source of Gonadotropic Hormones in the Urine.

If it is accepted that the hormones in the urine of pregnancy are different from the hormones of the anterior pituitary, the site of formation of the urinary hormones becomes a matter of great interest. This site has not yet been definitely located and the battle is still raging between those who believe in the placental origin of these hormones, and those who believe in their pituitary origin. Evans supports the latter view, chiefly because he finds that a large excretion of prol-an immediately follows castration in the normal animal. In these cases there is no ovum present so the possibility of a placental origin is rul-

ed out. Opponents of this view bring forward the cases of hydatidiform mole and chorion-epithelioma in which the prolan excretion is greater than in pregnancy and disappears on removal of the tumor. Also a case has been reported in which there was no excretion of prolan during pregnancy and in which there was an unusually thick boundary zone of fibrin between foetal and maternal tissues which was supposed to have prevented diffusion of prolan from the placenta to the maternal blood. The oft-quoted finding that the human pituitary is almost devoid of gonadotropic hormones during pregnancy has been used by both sides to support their views. The fact that the gonadotropic hormones are excreted in the urine, and are absent from the pituitary, during pregnancy, only in humans, apes and horses, and that these are the only animals in which the placenta is known to contain these hormones, also points to the placental origin of the prolan of pregnancy. Cameron tentatively suggests that the urinary and placental hormones are identical and that they differ from the pituitary hormones. Collip and Thomson suggest that, in the primate, the placenta has taken over some of the duties which are performed by the anterior pituitary in lower animals. The crucial experiment of hypophysectomy in the pregnant primate has apparently not been reported yet.

It seems probable that both these opposing schools will eventually be proven to be right. There is growing evidence that the prolan of pregnancy differs from that found in the urine in other conditions. Thus Evans has found substances in the urine in a case of teratoma of the testis which very closely resemble the anterior pituitary gonadotropic hormones. Also the urine at the menopause has been shown to contain some substance having properties very like the pituitary synergist. It is possible that, in primates and perhaps in the horse, gonadotropic hormones of placental origin are excreted

in the urine during pregnancy while at other times the hormones in the urine are from the pituitary gland.

In this discussion, five distinct hormones have been mentioned, namely, APH.A, APH.B, the pituitary synergist and prolan A and B. Not all workers would agree to this number of hormones and it must be admitted that, in some cases, the evidence upon which they have been separated is not conclusive. The role of those hormones in the various epochs of sexual life is briefly as follows:

Period of Sexual Activity.—During the years of sexual activity the anterior lobe of the pituitary gland controls the cyclic activity of the ovary by means of the hormones APH.A and APH.B. Through the medium of the ovary and its two hormones, oestrin and progesterin the pituitary is able to control the sexual cycle in the uterus. The inhibitory effect of oestrin upon pituitary secretion is also an important part of the reciprocal pituitary-gonad control. The existence of a specific anterior pituitary hormone which causes menstrual bleeding seems very doubtful. Hartman suggests that oestrin plays the most important part in the control of menstruation but that the anterior pituitary is probably also necessary.

The fact that there is a cyclic alteration in the activity of the pituitary gland corresponding to the sexual cycle has been shown by the demonstration of cyclic changes in its histology and hormone content. The cause of these changes in the gland is unknown, but it is suggested that the gland is under nervous control from some centre in the brain.

Puberty.—Since it has been shown that the pituitary controls ovarian activity during active sexual life, it would be natural to suppose that puberty occurs when the pituitary begins to secrete the gonadotropic hormones. It is possible that this is the case although it has been shown that the pituitary gland contains the gonadotropic hormones long before puberty.

It is also known that the sensitivity of the ovary to the gonadotropic hormones increases rapidly just before puberty. The onset of puberty is probably determined by the combination of an increasing secretion of gonadotropic hormones and increasing sensitivity of the ovary to these hormones. There is some evidence of an antagonism between the growth and gonadotropic hormones of the pituitary and a decrease in the secretion of the growth hormone coinciding with the increase in the secretion of the gonadotropic hormones has been suggested.

The Menopause.—At the menopause it seems probable that the conditions at puberty are reversed. The pituitary secretes less of the gonadotropic hormones and the ovary becomes less sensitive to them. This idea is based on the evidence that the pituitary contains the hormones long after the menopause, and A.P.H.A. and possibly the pituitary synergist are excreted in the urine in increased amounts; while the ovary can still respond to large doses of the gonadotropic hormones.

Pregnancy. — The relationship of the anterior lobe of the pituitary gland to pregnancy is by no means clear. Hypophysectomy has been done in pregnant animals of various species with widely divergent results. In rabbits it is well established that the pituitary is essential for the maintenance of pregnancy. In the cat, rat, mouse, and guinea pig it is equally certain that the pituitary can be completely removed at mid-pregnancy without producing abortion and in many cases normal or delayed delivery of living young results. It is impossible to predict from these experiments what role the pituitary plays in pregnancy in the human and the ape, since it is already clear that its role in these species must be somewhat different to that in lower animals.

Lactation.

Early experiments, which showed that denervation or even transplanta-

tion of the lactating mammary gland did not interfere with its function, suggested that the factors controlling lactation were blood borne. When the ovarian and anterior pituitary sex hormones were discovered, interest centred upon them as possible factors in the control of lactation.

The present position on this subject is by no means well defined. Species differences in the reaction of the mammary gland are particularly troublesome. However, the mechanism controlling the mammary gland may be briefly outlined thus. Oestrin, produced in the ovary or placenta, brings about development of the duct system of the glands. It is unable to produce development of the alveoli or secretion of milk except in the guinea pig. Progesterin, the hormone of the corpus luteum, produces development of the alveolar structure of lobules of the gland after the duct system is developed but it also does not produce secretion. Thus oestrin and progesterin are classified as formative factors as opposed to the functional factor which produces secretion. There is some evidence that, in the ovariectomized animal, these formative stimuli may be supplied to the glands by the pregnant uterus, since development of the glands and even lactation can occur if the ovaries are removed early in pregnancy.

There is now satisfactory evidence that the normal functional stimulus to the mammary glands comes from the anterior lobe of the pituitary gland. The active substance seems to be a separate hormone and is known as prolactin or galactin. This hormone acts on the mature gland to cause the secretion of milk. A continuous supply of the hormone is necessary to maintain lactation since the flow of milk stops very rapidly when the pituitary is removed even though the young continue to suckle. It is interesting that, in the hypophysectomized animal, the emptying of the pregnant uterus supplies a functional stimulus to the mammary gland which results in transient

lactation. This stimulus may be due to the placenta or to the mere mechanical emptying of the uterus.

The clinical observation of the importance of stimulation of the breast in the maintenance of the flow of milk has been confirmed experimentally. It has been shown that the effect of nursing is largely attributable to the mechanical stimulation of the nipple rather than to emptying of the breast. Glands in which the nipple is removed soon atrophy whereas glands in which the lactiferous ducts are tied but nursing is continued remain active for weeks. There is some evidence suggesting that this mechanical stimulation acts by increasing the output of prolactin from the pituitary. The afferent side of this mechanism is, so far, unknown.

The mechanism of the control of lactation in the human during pregnancy is probably somewhat as follows; although the danger of arguing from analogy should be borne in mind, since much of the experimental work has not been confirmed in humans. During the first half of pregnancy oestrin and progestin act on the gland to bring it to the mature state. During this time there is no secretion of milk because oestrin seems to inhibit the secretion of prolactin in addition to having a direct inhibitory effect on the mammary gland. During the second half of pregnancy the oestrin content of the blood falls slowly and the mammary gland shows histological signs of secretory activity. Immediately following delivery the oestrin content of the blood falls rapidly and prolactin is secreted by the anterior pituitary. This, together with a possible stimulus directly from the uterus, initiates the secretion of milk. Regression of the corpus luteum may also be a factor in producing this activity of the pituitary. Throughout lactation, the supply of prolactin, and hence the supply of milk is maintained by the mechanical stimulation of the nipples involved in suckling.

Prolactin has definitely been shown to cause, or accelerate, lactation in the mature mammary gland of many species of animals as well as in women. In a group of cases in which the clinicians were convinced that no further improvement in milk output would have occurred under normal circumstances, the intramuscular injection of prolactin produced an increase in milk output of 50-400 grams per day in 25 out of 29 cases.

Posterior Pituitary.

The posterior lobe of the pituitary gland is chiefly of interest in connection with reproduction because of the secretion of oxytocin and its possible relationship to labour. Since the technique for hypophysectomy has been perfected it has been shown that normal delivery of living young may take place in some species in the absence of the pituitary gland. Smith has even shown that, in rats, following removal of the posterior lobe alone, normal mating and parturition is possible. These experiments seem to indicate that the role of oxytocin in the initiation of uterine contractions at term has been overestimated. On the other hand, repeated pregnancies, in the rat, cause enlargement of the posterior lobe without affecting the anterior lobe of the pituitary.

Anselmino, Hoffman and Kennedy have recently suggested that the toxic albuminuria of pregnancy or eclampsia is due largely to an oversecretion of the antidiuretic and pressor principals of the posterior pituitary. They found substances present in the blood in eclampsia whose physical and chemical properties were identical to those of the posterior pituitary hormones. They were also able to reproduce, experimentally, nearly all the important clinical signs of the condition, such as water retention, rise in blood pressure, kidney changes, fits, etc., by the use of posterior pituitary hormones.

Clinical Applications.

A complete review of the clinical use of endocrine products in gynaecological practise would be entirely beyond the scope of this paper, but a few comments upon the bearing of recent experimental work on the clinical use of the various hormones may be in order.

Of all the hormones which have been discussed, oestrin in a variety of forms, and prolan from pregnancy urine are the only ones which have been given extensive clinical trial. The corpus luteum hormone and the hormones of the anterior pituitary have only very recently been made available for clinical use. In view of Engle's work with monkeys, it is not surprising to find that the clinical results obtained with prolan have been rather disappointing. Some successes in cases of pituitary infantilism and in certain disorders of menstruation have been reported. It seems obvious that greater success should be expected, especially in those cases which are classed as hypogonadism, from the use of the hormones of the pituitary itself or from the use of prolan combined with the pituitary synergist. Evans suggests that this pituitary activator or synergist combined either with prolan or with the gonadotropic hormones of the pituitary will "probably prove to be the supreme agent for gonadotropic therapy in the future."

It would appear that, in the higher apes and in man, the hormonal control

of reproductive functions is radically different from that in the lower animals, at least in so far as pregnancy is concerned. This difference emphasizes the need for clinical rather than laboratory experimentation and points to the danger of arguing from analogy with the lower animals. More extensive use of the actual hormones of the anterior pituitary in clinical practise seems to be the most promising line of endeavour in the field of endocrinology at present.

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PHYSICAL HABITUS AND MENTAL CONSTITUTION

By B. H. McNEEL, B.A., '36.

The relationship between personality and certain physical characteristics has long intrigued the fancy of mankind and has found a place in common thought, so that you may have heard it said of your favorite Titian: "I might have known she'd have a temper like that with that red hair." As ardent disciples of science we are likely to discount such fancies as superstition, and even to consider the classical rotundity of a Falstaff, the ascetic leanness of a St. Augustine, or the athletic beauty of a Galahad, as mere coincidences.

Ancient philosophers in various civilizations had various classifications of physical habitus with which they sometimes linked definite mental characteristics. In the modern era men of science have made similar classifications. Perhaps the most interesting classifications of physical types from a medical point of view are those which indicate functional peculiarities and those which indicate specific diatheses. Among the former is the classification of Rotan, 1828, of the types "musculaire," "digestif," "respiratoire," and "cerebrale," suggesting a development of definite organs commensurate with their function. Among the latter is that of Rokitansky, who describes, (1) a normal type subject to unconstitutionally diseases only; (2) a hyperplastic type with a predisposition to carcinoma; (3) a hypoplastic type with a predisposition to tuberculosis. More non-committal and generally useful for purposes of anthropological and clinical study are Kretschmer's types—pyknic, athletic and asthenic. These are based on apparent skeletal relations and relative development of tissues and may be described briefly thus:

Pyknic—a type showing marked development in girth at the expense of height. The contours of face and body are soft, smooth and rounded.

Athletic—a type showing marked development of skeletal, muscular and skin tissues. The contours conform to the outlines of the muscular tissues. The body tapers from the shoulders and the height is above average.

Asthenic—a linear type of rather narrow and shallow build giving the impression of long, thin limbs with poor development of muscle and subcutaneous fat. Contours of face and body are, in general, angular. To these three he adds the dysplastic type, showing variations due to endocrine imbalance. These include abnormalities of height, of limb length, of distribution of subcutaneous fat, of distribution of hair.

Kretschmer's types are averages of recurring forms. Each individual deviates from the average for his type to a greater or less degree so that the "classical" type is the exception rather than the rule. A study of any population shows extremes of marked pyknic or asthenic build and between these extremes a gradual transition through pyknoid, athletic and athletic—asthenic types. If a graph be plotted with the number of cases as the ordinate and some measure of the physique (e.g. a morphologic index) as the abscissa a normal distribution curve is obtained. The mode of this curve falls within the range of the athletic type.

Kretschmer made extensive studies on patients suffering from psychogenic mental disease and he concluded that, in the Manic-Depressive and Schizophrenic groups, the majority of individuals of pyknic types had a tendency to a cycloid personality and normal ath-

letics and asthenics to a schizoid personality. He named them cyclothymes and schizothymes and these correspond fairly well to Jung's extroverts and introverts or to the syntropic and idiotropic personalities of Wertheimer and Hesketh. These classifications of personality are based on observations of two definite tendencies in individuals with reference to their environment. Probably no individual is purely extroverted or purely introverted but in designating any type the predominating characteristics of his personality are considered. Some must be designated "mixed type" as the more dominant trend cannot be determined.

The natural and true conception of the individual as a unit may readily be forgotten in the intensive study of any one aspect of the individual's existence. Wertheimer and Hesketh define the human constitution as "the correlative unity of those morphological, physiological and psychological developments of the individual which are definitely more influenced by heredity than by environment." Draper speaks of the human constitution as consisting of four panels—the anatomic, physiologic, psychologic and immunity panels. He goes on to show a definite relation between anatomic and corresponding pathologic panels. Here we are carried back to the conception of the interrelation of form, function and diathesis. With the growing popularity of Bacteriology at the end of the last century and the conception of causation of disease by micro-organisms the importance of constitutional studies was forgotten. With the development of Bacteriology and studies in immunity interest in the constitution has been revived. However, it is difficult to imagine that anyone will ever be rash enough to repeat di Giovanni's assertion that the physical habitus is the determining factor in the type of disease. Rather say that a common factor may determine both form and diathesis.

Kretschmer's work is the classical work on physical habitus and mental constitution. However, his methods were too complicated and inexact for

general use. A number of workers, notably Wertheimer and Hesketh, have endeavoured to investigate the problem by the use of one or more simple morphological indexes. The details of the structure and use of these may be obtained from the papers noted below. Wertheimer and Hesketh evolved an index based on di Giovanni's principal that the impression type depends on the relation of the size of the body cavities to the limb length. This index is a very useful one, as is also the sub-costal angle measurement used by the Ann Arbor School.

In conclusion a brief summary of the findings of various investigations may be given:

There is a definite relation between pyknic and pyknoid body types, extrovert personalities and Manic-Depressive Psychoses and between athletic or asthenic body types, introvert personalities and Schizophrenic Psychoses. In many cases where there appears to be a contradiction to such a relationship the fault is found to lie in diagnosis or in failure to regard the age group. The age factor is of importance in the development of the body type and in complicating the picture with atypical conditions such as arteriosclerotic depressions. The pyknic type is said not usually to develop until about the age of thirty and to reach its most typical form before the end of middle life. Some observers maintain that the true asthenic type becomes more marked after middle life while the athletic type in middle life and even earlier may assume certain pyknic characteristics. In any case, due to the known indefinite nature of body types and the still uncertain definiteness of mental types nothing better than a 75% correlation can be expected.

The above statements apply more specifically to men than to women, for in the latter there is even greater indefiniteness of types.

It is to be expected that more light will be thrown on this subject in the future by statistical studies in anthropology, psychology, psychological medi-

cine and genetics undertaken for other purposes and relating to the development and progress of individuals and families in a more or less normal population.

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HOW FAR SHOULD STATE HEALTH DEPARTMENTS GO?

Baby's Proper Feeding the Doctor's Problem. One of the most frequent inquiries received by the State Department of Health is that concerning an infant's diet. It is, of course, impossible for the Department to advise or give suggestions regarding a suitable diet for any infant. It apparently is not generally realized by the laity, that food requirements vary for every infant. One infant may thrive on a given food while the next will not tolerate it. Consideration must be given to the fundamental requirements of each infant such as the protein, fat, carbohydrate, water, mineral and vitamin requirements. So far as is known, breast milk is the only universally suitable food for infants. If a baby is deprived of this he should be taken to the family physician and placed on a proper feeding. It is only after a thorough history has been taken and a thorough physical examination has been made that the proper food can be advised for any infant. It is quite obvious that such service is out of the realm of the State Department of Health.

The Department, however, has literature on infant care that is available on request. The Children's Bureau at Washington also publishes some excellent pamphlets on infant and child care which should be read by every mother who wishes to give her child the best of care and training.—From Ohio Health News, Nov., 1934.

THE TREATMENT OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

By PAUL HAMILTON, B.A., '35.

The treatment of this dread complication of Pernicious Anaemia is just beginning to be placed upon a sure footing. With the advent of liver therapy as a result of the work of Whipple and Minot and Murphy in 1926, the results in relation to the anaemia were very gratifying. It was found that the signs and symptoms of pernicious anaemia could be cured and controlled by liver administration and that patients, even in a comatose condition could be restored to clinically good health by this dietetic form of therapy. The treatment of pernicious anaemia is, pure and simply, adequate liver for the needs of the individual.

Attention was next directed towards the results of the effect of liver therapy on Subacute Combined Degeneration of the spinal cord with its associated signs and symptoms. For a while the results were conflicting, cures being reported in some quarters with remarkable results, while elsewhere it was claimed that the disease was only held in check or made progress even after the continued exhibition of liver.

The most important contribution to date in the literature is the analysis by Ungley and Suzman in 1929 of their 61 cases of pernicious anaemia, of which 30 developed subacute combined degeneration of the spinal cord. Five deaths occurred in four years. Their results were obtained by using 1½-2 lbs. of liver per week, amounts which were not used by other workers, nor have been up to the present time except in certain centres.

But at the present time there is available the results of treatment of cases of subacute combined degenera-

tion at the Toronto General Hospital.* For the period 1926-1933 records have been kept dealing with 172 cases of pernicious anaemia, of which 74 showed signs and symptoms of subacute combined degeneration; of these 8 died within a few days or weeks of admission to hospital and hence did not receive a fair course of liver therapy. That is, then, the results of the effect of liver therapy upon subacute combined degeneration in 66 cases can be observed and analysed. The results of treatment are very gratifying indeed and establish upon an undisputed basis the fact that adequate liver is effective in the treatment of subacute combined degeneration.

A word here as to what is meant by "adequate" liver is not out of place. Some workers state that ½ lb. a day or its equivalent is adequate, others claim 1-2 lbs. a week are adequate. In this paper, adequate is defined as the amount of liver or its equivalent necessary for the individual patient which will give the maximum clinical cure. It matters not whether the "adequate" amount is ½ lb. a week or 4 lbs. a week. It is the needs of the individual patient that count and no specified amount can be used.

It is assumed here that the liver is given in such fashion that its potency is not greatly interfered with. It is obvious that liver preparations of lesser potency will have to be given in larger doses than the more potent preparations. Let us restate our definition of "adequate" and state that the pa-

*The results here summarized are those of Dr. Farquharson, Dr. Hyland and Dr. Dauphinée, under whose direction this work has been carried on at the Toronto General Hospital.

tient must receive adequate quantities of anti-anaemic factor for his own needs, be it a small or large amount.

This is an important fact which has been established. Practically it amounts to, "give the patient liver, or its equivalent and if no response occurs, give more; if still no response, give more." There are no ill effects from large doses of liver and to date there has been no contra-indication to its free use. Another question of importance is how long to continue these large doses. That depends upon the patience of both physician and patient. But at any rate treatment should be persevered with for at least 2-3 years. For some cases are on record that have not begun to make much improvement until the lapse of a year's intensive treatment with subsequent marked betterment over a period of a year or so.

There are some rules, however, which will guide the magnitude of therapeutic endeavours. It has been found at the T.G.H. that the initial treatment of pernicious anaemia can be started on $\frac{1}{3}$ - $\frac{1}{2}$ lb. whole liver per day, or the broth or extract of 1 lb. whole liver per day by mouth, or the extract as prepared by the Connaught Laboratories, from 100 gms. of liver intramuscularly per week. When the patients show signs and symptoms of subacute combined degeneration this dose is doubled. This treatment is given in a 3 months' course, consisting of hospitalization, complete rest in bed, liver therapy as above, with re-education of the patients' disturbed motor function by physiotherapeutic measures. At the end of this time the patient is, if possible, discharged and brought back to the clinic once a week for the administration of liver. The dose of liver is then varied, depending on the needs of the patient and may be increased or decreased till the maintenance dose is determined.

For the treatment of subacute combined degeneration the intramuscular route is deemed the most advisable,

firstly because the patients cannot tolerate such large quantities of liver by mouth, and secondly, by having the patient come to a clinic it is rendered certain that he gets his liver, for however obliging the patient is, yet his word is not often of much value when it comes to eating large quantities of liver. In summary then we may say that the treatment of subacute combined degeneration is as follows:

(1) 3 months' rest in bed as a minimum.

(2) Adequate liver as defined above.

(3) Re-education of motor disabilities

Results of Treatment.

This may be considered under two heads, namely, the changes in the pathological picture, and the changes in the clinical picture.

The changes in the pathological picture of subacute combined degeneration are not striking. The main fact seems to be that, in the presence of the specific factor, normal gliosis occurs in the areas of the cord which showed degeneration before. In fact this is the only noteworthy change. It is true that, before liver is given the cord may be somewhat full and swollen, and after liver, it appears smaller and shrunken in places, but this is due entirely to the replacement of degenerated areas by glial tissue. The blood picture and bone marrow also return to normal, and the accompanying glossitis, if present, also clears up. There is no change in the condition of the gastro-intestinal tract over its previous state.

Before discussing the results of treatment, it is well to state here that diagnosis of subacute combined degeneration is made only in the presence of subjective and objective disturbances. Hyperaesthesia alone or numbness and tingling or impaired joint sense, taken singly may indicate nervous changes, but for the sake of safety, in order to eliminate errors,

diagnosis is made only in the presence of clumsiness or weakness of the limbs with two or more of the following signs, viz., impaired vibration sense, impaired sense of position of joints, impaired or absent tendon reflexes, impaired sphincter control, impaired superficial sensation with or without mild pyramidal tract disease. Such cases are considered to be *mild*. A case of *moderate* severity can be thought of as one with severe posterior column disease with little or no pyramidal tract disease or moderate involvement of both posterior columns and pyramidal tracts. *Severe* cases have well advanced posterior column and pyramidal tract disease with gross spasticity or ataxia predominating and are usually bedridden.

The response may be *marked* with freedom from symptoms and improvement in the objective neurological signs, *moderate* with definite improvement in symptoms with little or no change in the physical signs, or *slight* with little or no change after a 3 months' course, but no progression of the disease. In viewing the results of treatment, it is well to bear in mind the following facts: first, that the longer the disease has been manifest, the more refractory it is to treatment. Second, the severity of signs and symptoms bear no seemingly correlated relation to the pathological changes. Third, the reason for the improved condition is not known, but may be due to restoration of function of nerve channels which though inactive are yet capable of having some function restored. It may also be due to the remaining fibres, being able to take on added work and so carrying a heavier burden than normally.

The results of treatment of these 66 cases followed at the T.G.H. for the period of 1926-1933 yield the following information. All the patients complained of paraesthesiae in some form or another, and of these, 44 showed marked improvement, 15 showed moderate improvement and 7 showed slight improvement or remained stationary. None were made worse. The

results in impaired joint sense are very similar, though only 61 of the cases showed this disability. This disturbed function is the earliest sign to show improvement. In marked contrast is the improvement noted in those cases showing impaired vibration sense. All of the cases exhibited this sign to greater or lesser degree and of these 49 showed only slight improvement or no change, but none became worse. That is, once this latter condition has become established, it is likely to remain; but there are marked exceptions, however. Its return is a very consistent and valuable sign, but it reappears very slowly. It is also worthy of note that impaired vibration sense is found about three times as often in the lower limbs as in the upper limbs.

To this triad of paraesthesiae, impaired vibration sense and impaired joint sense, may be added the fourth most common symptom, disturbed gait. This may be spastic, ataxic or a mixture of both, about half the cases showing ataxic manifestations while the pure spastic disability is the least common. Improvement in gait may be expected in practically every case, the best results being obtained in the ataxic and spastic-ataxic forms. About 70% of the cases showed a marked improvement. Part of the good return of motor function is due, of course, to re-educational and physiotherapeutic measures, and part due to the general improvement in health, and increased constitutional well-being. Tone in the muscles is also restored considerably, and as above stated, the functional capacity of the nervous system is greatly enhanced.

These four signs, paraesthesiae, impaired vibration sense, impaired joint sense, and disturbed gait are the most constant symptoms to be found, and with the exception of the vibration sense, are all very markedly improved by liver therapy.

Impaired superficial sensation occurs in about 2/3 of the cases, is segmental in type and is markedly improv-

ed in most instances. Improvement is least in the most marked forms. The impairment tends to be a dissociated one, pain sensation being most affected, temperature and light touch least.

Sphincter disturbances were noted in 36 cases, and of these 26 or 70% showed marked improvement. The ankle jerks were diminished or absent in 34 cases, while exaggerated leg reflexes were noted in 26 cases. Both these latter conditions were benefited only slightly or not at all by treatment, but were at least kept from getting worse. The knee jerks were diminished or absent in 19 cases, of which 50% showed marked improvement. Clonus was noted in 8 cases, with marked improvement occurring in 6.

There are some interesting points in connection with associated psychic manifestations. Of the 66 cases, 33 showed definite psychic disturbances. Of these, 19 showed marked improvement, 6 moderate improvement and 2 slight improvement. The remaining 6 cases became definitely worse under treatment. Those which improved only

moderately were of an age which made them possible candidates for senile changes. Of the 6 which became worse, two had previous mental history. This finding is in accord with other such cases reported in the literature, but no explanation has as yet been proffered.

The results of treatment may thus be summarized. The paraesthesiae, impaired joint sense, disturbed gait, impaired superficial sensation, sphincter disturbances, psychic manifestations and clonus are, by and large, markedly improved. Impaired vibration sense, absent or reduced tendon jerks and exaggerated leg reflexes are in general not much improved, but changes for the worse are stopped. Psychic disturbances may develop in the course of the treatment.

In conclusion the writer wishes to express his indebtedness to Dr. Farquharson, Dr. Hyland and Dr. Dauphinée at the Toronto General Hospital for access to their records, and especially to Dr. Hyland for the free use of his unpublished analysis which has here been briefly summarized.

CHRONIC TRAUMATIC SUBDURAL HAEMATOMA

By ALLAN A. BAILEY, '35

Subdural haematoma is an important and not uncommon intracranial lesion which until recently has not received the attention it merits. Most text book descriptions are inadequate and for this reason it was thought justifiable to briefly review the more important clinical features of the condition.

Definition.

In a typical case the history is obtained of a slight injury to the cranium followed by a latent interval of several weeks or months before mental changes, headaches and neurological signs appear. The lesion consists of a collection of blood, surrounded by a distinct mem-

brane, between the dura mater and the arachnoid. At present it is felt that the condition should be distinguished from pachymeningitis haemorrhagica interna which it simulates clinically except that in the latter there is no history of injury.

History.

A complete review is impossible here, but those interested will find more details in a paper by Cushing and Putnam.¹ 1559—Pare reports the case of Henry II. of France, who died following a supra orbital wound. 1817—Haussard described the clot and membranes.

1857—Virchow published a paper and described clearly the histopathology. He distinguished between subdural haematomas of traumatic origin and a spontaneous variety which he called pachymeningitis haemorrhagica interna.

Following this many cases were reported but from a clinical point of view the paper by Trotter² in 1914 is the most important discussion of the condition. He emphasized trauma as the aetiological factor and considers the relation between traumatic subdural haematoma and pachymeningitis haemorrhagica interna.

1925—Cushing and Putnam reviewed the literature and discuss the subject in a thorough manner.

1922—McKenzie³ described eleven cases and emphasizes certain principles in treatment.

Incidence.

It is difficult to get data upon this point, as the condition has been given little attention in the text books, and its frequency has not been appreciated until recently. Also prior to the development of the present technique in neurosurgery and neurological investigation, the condition was exceedingly difficult to diagnose except at autopsy.

Munro⁴ states this occurs in one of every six cases of craniocerebral injury, and Kaplan⁵ believes that it is more common than middle meningeal haemorrhage.

At the Toronto General Hospital since 1926 there have been twenty cases of traumatic subdural haematoma and two hundred and seventy cases of cerebral haemorrhage. In the autopsy records at the Toronto General Hospital since 1925 there were one hundred and fifteen cases of subdural haemorrhage and one hundred and eighty-seven cases of cerebral haemorrhage. It should be noted that it was not determined in what per cent of the former traumatic subdural haematoma was the cause of death.

It is very difficult to assess the significance of these statistics at the present time but it is sufficient to point out that the condition is not rare.

Aetiology.

Trauma is the important cause, but some authors state that alcoholism, and disease of the vessel wall, either arteriosclerotic or syphilitic, are predisposing factors. The latter would appear to be important in a few cases.

It should be emphasized that the injury necessary to produce the lesion is relatively slight, rarely sufficient to produce a fracture, and is usually received in the occipital or frontal region. The reason for the latter is evident when one remembers that transverse movement of the brain is restricted by falx cerebri while no such protection is given in the antero-posterior direction. The superior sagittal sinus is fixed, and the veins enter it from the brain, which is moveable. Thus it can be understood how a blow which causes a sudden movement of the cerebrum might cause a rupture of one of those veins.

Pathology.

It is on the basis of the clinical history and the pathology that traumatic subdural haematoma is distinguished from pachymeningitis haemorrhagica interna and it is not intended to enter upon a discussion of the difference in this paper.

At operation or autopsy the dura has a brown or blue green tint and incising it a cyst is found. The part of the cyst wall adherent to the dura is tough and thick while the part next the arachnoid is thin, translucent and only slightly attached to the arachnoid. There are numerous small blood vessels on the inner wall of the cyst. The cyst is longest in its antero posterior diameter and contains blood, partially clotted blood or decolourised fluid. The surface of the brain underlying the cyst is slightly deformed

and the convolutions of the opposite hemisphere may be flattened by pressure. Occasionally the blood in the cyst becomes organized.

Causation of Symptoms.

Trotter² discusses this in a manner readily understood and an attempt will be made here to follow briefly his reasoning.

The cranium cannot expand, and if the space within it is being filled under pressure some of the contents will be displaced. First, some cerebro spinal fluid is removed and as the pressure increases the veins are compressed. However since the sum of their cross section is greater than that of the arteries a certain degree of compression may take place before venous stasis occurs. At this point there will be a slight disturbance of function, but the instant anaemia of the capillaries takes place function ceases. If the anaemia develops slowly paralytic symptoms will not be so marked as if it occurred suddenly, as there is a physiological compensation for the disturbance. Nevertheless, there is finally a point in this toleration of pressure at which, if the slightest increases takes place, the scale tips, as it were, and all the symptoms of loss of function appear at once. Normal variations in blood pressure are sufficient to do this.

The cause of the long latent interval is a controversial point and much experimental work has been done in an attempt to prove one explanation or another. Trotter emphasizes an important point when he suggests that there is some factor other than size, shape and situation, of an intracranial lesion which influences the clinical picture. He believes this factor to be the rate at which the lesion develops. The haemorrhage usually takes place from a small vein, and the difference of the pressure in the veins and that in the subdural space is not great. Thus the amount of haemorrhage will depend on that difference,

plus the rate at which thrombosis of the vein develops. However, it is not at this point that symptoms appear which warrant detailed investigation. It is interesting to note that no one has been able yet to produce experimentally the same pathological picture in animals by injecting blood under the dura. In all cases the blood was reabsorbed as it is elsewhere in the body. There is no explanation as to why the clot is not organized and reabsorbed in the type of case under discussion. This much seems clear, that the blood is enclosed by a definite membrane in a few hours after the rupture of the vessel, and that the lesion increases in size during the next few months.

On the basis of experiments Gardner⁶ believes that this increase can be accounted for by osmosis. There is present in the cyst proteins and broken down products which will not pass through a semi-permeable membrane like the cyst wall. He has shown that the osmotic pressure within the cyst is greater than in the subarachnoid space, and Munro⁴ confirmed his results on some patients. Thus fluid is gradually withdrawn into the cyst, and its size increases. If this be true, then we have an explanation of the latent interval before symptoms develop.

Trotter² considered a slow or intermittent bleeding from the responsible vessel to be the explanation. Putnam and Cushing¹ thought there might be repeated haemorrhages from the vascularised granulation tissue of the cyst wall.

Clinical Picture.

The sequence of events is usually something like this: a man receives a slight blow on the head usually in the occipital or frontal region and it may or may not produce unconsciousness. He recovers quickly and in a few minutes goes on with whatever he is doing. In the next few days he may have some headache but usually not

sufficient to cause him to see a doctor. Then in three to eight weeks he complains of headaches, is somewhat irritable, drowsy and in a general way his personality is different. Neurological examination at this time will likely be negative and the cerebrospinal fluid has a normal pressure and appearance. It is at this stage of the condition that an encephalogram is of great value.

Suddenly the picture changes, the patient passes into a semi comatose state and on careful examination some alteration in the nervous system will be demonstrable. These neurological signs vary from case to case but in practically all cases they suggest an upper motor neurone lesion. An analysis of seventeen cases at the Toronto General Hospital was made with a view to determining the relative frequency of certain neurological signs and subjective findings. This is shown in the following table:

	Number of cases	Percent of total
Total No. of cases.....	17	100
History of injury	14	82
Unconscious after injury.	9	53
Admitted conscious	12	70
Semi comatose	5	29
Blood pressure above		
140 systolic	9	53
95 diastolic	5	29
Neurological signs	17	100
Altered pupils	3	17.6
Optic neuritis	14	82
Paralysis	13	76
on opposite side	8	47
on same side	4	24
on both sides	1	5
on neither side	4	24
Reflexes altered	10	59

In evaluating the significance of certain findings in the foregoing table it is important to realise that the series of cases is small. It should be noted that optic neuritis is not reported so commonly in other series while some neuro surgeons report a higher frequency of pupillary changes. Also some of these patients were under observation a week before any neurological changes were present. In only two cases was aphasia present despite

the fact that there were twelve left sided lesions.

Differential Diagnosis.

The problem here of course changes with the progress of the condition. It is convenient to divide it into three stages: first immediately following the injury, second during the latent interval preceding the third stage when he is unconscious or semi comatose.

If the patient is seen in the first stage and is unconscious the problem may be considered concussion so that only careful observation will indicate what is to be done. He will recover and careful examination will not reveal the necessity for specific neurological diagnostic procedures. Since the cause of the condition is relatively common and the condition comparatively infrequent, it is unwise to suggest any possible future symptoms. Post traumatic neuroses are sufficiently common without encouraging them.

The patient may come during the second stage complaining of headache and drowsiness. His friends state that his personality is different, that he cannot concentrate and that his behaviour is somewhat childish. The patient is correctly oriented and there are no hallucinations or delusions present. The diagnosis at this stage may be very difficult as there are usually no neurological findings and unless a history of injury is obtained the condition may not even be suspected. To distinguish it from brain tumour the history of injury is important, and the fact that mental symptoms are more common in traumatic subdural haematoma is also of value. If the condition be suspected then an encephalogram is of inestimable value and even then it may be impossible to distinguish it from brain tumour. It should be emphasized that in either case surgery is indicated and that the important thing is to establish the presence of tumour whether neoplasm or haematoma.

The doctor may be called to see the patient in coma and again the difficulty is to differentiate the condition from brain tumour or some cerebral vascular accident. In this stage the neurological signs outlined above usually appear; these are of the upper motor neurone type and may be the same as found in an internal capsule lesion. However in the latter, the onset of symptoms is sudden, rather than gradual as in subdural haematoma and brain tumour. Unequal pupils and optic neuritis are quite common in the condition under discussion. The history of injury, headaches and mental symptoms preceding the onset of coma aid in the diagnosis, particularly in distinguishing it from brain tumour. Even then it may be impossible to arrive at a diagnosis until a bilateral trephine is done. Occasionally there are haematomas on both sides. Spinal puncture yields no information and should not be done if optic neuritis is present. It should be remembered that with increased intra cranial pressure due to any cause, albumin, sugar, or both, may be found in the urine. If the condition follows an alcoholic bout, casts may be also present and with an increased blood pressure the diagnosis is somewhat more complicated. Again if there is any doubt trephine is indicated.

Treatment³.

When the diagnosis is established, operation should be carried out at once as nearly all cases recover when subjected to operation. A small opening in the bone over the suspected area is made, the dura incised and contents of the cyst sucked out. Normal saline is put in and small drainage tubes left in for a day or two.

The mortality in those not subjected to operation is for practical pur-

poses 100%. In the cases reviewed for this paper 88% were operated upon and of these 85% were cured.

Summary.

1. The condition is not infrequent among cerebro-cranial injuries.
2. Mental disorders occur more frequently in the presence of this lesion than in any other space filling intra-cranial lesion.
3. Clinically—a history of injury, latent interval, headaches, drowsiness, personality change and finally coma.
4. An accurate clinical history is of great importance in the diagnosis of this condition.
5. The importance of finding a cause for all symptoms.
6. The more general use of encephalography will make the condition more frequently recognized.
7. Bilateral exploratory trephine may be necessary to establish diagnosis.
8. Treatment—small opening, evacuation of cyst, drainage, usually followed by recovery.
9. The prognosis for recovery is good if cases are diagnosed during life and subjected to operation.

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I am indebted to Dr. K. G. McKenzie for the opportunity to analyse the histories of a number of his patients. Dr. Hyland criticised the paper and made a number of helpful suggestions for which I wish to express my gratitude.

AN HISTORICAL OUTLINE OF APPENDICITIS*

By GEO. C. STEVENS, '27.

The year 1866 marks a turning point in the consideration of morbid conditions occurring in the right iliac fossa. Prior to this year many different abdominal disorders localizing in the right iliac region were recognized, and were known by as many different names. Thus perityphlitis, caecitis, etc., were names which littered the contemporary literature on abdominal diseases of this period.

In 1866 a Boston surgeon, one Reginald Fitz, in an article published in the *American Journal of Medical Science* of that year, by a clever recapitulation of the facts known up to that time, and a comprehensive report of a large number of cases coming under his own observation, so far changed the conception of right iliac disorders as practically to inaugurate a new school of thought on those conditions. A brief résumé of the various advances made in knowledge of the condition we now know as appendicitis will give a more clear understanding of the importance of the correlations and deductions made by Fitz, when viewed in the light of our present advanced understanding of appendicular derangements.

As early as 1711 a German anatomist, G. Wirgman, records a dissection made on the body of a malefactor in the public theatre at Altdorff. To quote: "I found the small guts very red and inflamed in several places," and a little later, "but when I was about to demonstrate the situation of the great guts, I found the vermiform process of the caecum prenatually black and adhering closer to the peritoneum than usual. As I was about to separate it by gently pulling it asunder, the membrane of the process broke and

discharged two teaspoonfuls of matter."

He generalizes his finding rather shrewdly. "This instance may stand as a proof of the possibility of inflammation arising and abcess formation in the appendix, which I have not observed to be noticed by other writers, and when in practice we meet with a burning pain where the part is situated, we ought to give attention to it."

Mestivier, a Frenchman, writing in 1759, gives us the first record of appendicitis observed during the life of the patient. This particular case is by way of being a classical one and might well stand a little detail at this point.

An elderly man sought relief for a growth in the right side of the umbilical region. Fluctuation was detected and a pint of pus was subsequently evacuated by incision. The wound readily healed by first intention, but unfortunately the patient later succumbed. Coming to autopsy the caecum was covered with small gangrenous patches, and the vermiform appendix was found to contain a very rusty and corroded pin.

To quote the report: "It is easy to understand that although the patient had never spoken of swallowing a pin, the one in question had been concealed for a long time in the vermiform appendix of the caecum, and that it was undoubtedly this which had irritated the different coats of which the organ is composed and given rise to all the patient's symptoms, finally causing the death which ensued."

Joubert Lamotte, a French medical student, in 1766 describes a case in which the patient died with supposed intestinal obstruction. The autopsy disclosed the caecum and appendix to be filled with small, round calcareous masses, considered by him to be cherry

*Reprinted from Vol. II, 1925, University of Toronto Medical Journal.

stones. In these so-called stones we have the first fecal concretions on record.

The nineteenth century medical literature is more replete with references to the appendix. Parkinson, a physician of London, in 1812 draws attention to the case of a child who died with all the symptoms of appendicitis as we know them, and on whom a subsequent autopsy revealed a perforated appendix. In this case we have the first record of a death from perforation of the appendix, and the subsequent sequelae.

A chemical analysis was made of fecal concretions found in an appendix by Wegeler in 1813. The true nature of the concretions was surmised as a result of the analysis, but the finding was not of much importance at this time.

Appendicular lesions came to take a more definite place in disease classifications about this time, however, the work of Louver-Villermay, a native of France, being the instrument of the moment. Villermay in 1824 published an article in a French medical journal containing the interesting report of two cases, in both of which the patients complained of sharp pains in the right iliac fossa, and of much vomiting. Death ensued in each case. Gangrenous appendices were found existing at both autopsies.

Villermay classified the symptoms with great accuracy, and the report he made subsequent to the autopsies opened up the way for the observations of another mind, one Métier, likewise a son of France.

Using the two cases recorded so carefully by Villermay, and citing as well three of his own, Métier points out that appendicular lesions by no means deserved the obscurity hitherto accorded them, as being somewhat of a rarity. Had not two of his cases come under the observation of one physician, and within a very short time of each other, and was he not able to cite three similar cases of his own

clinic? Surely such lesions were by no means unusual!

Métier draws attention to a case showing at autopsy an immense abscess, to which part of the caecum, together with the appendix, was adherent, the latter communicating directly with the abscess cavity. Comparing this with his acute cases, he says: "I am constrained to believe that here also the appendix caeci was the original source of evil. That there had been a collection of fecal matter in its cavity, perhaps even a stercoral calculus, and that the appendix, acutely inflamed, had become adherent to the peritoneum, the adjacent cellular tissue being engorged and an abscess forming in consequence of the perforation of the appendix."

In this viewpoint we have a clear recognition of the common causal relationship of the appendix and chronic suppuration in the right iliac fossa. The precepts advanced by Métier entitle him to all credit in first recognizing the chronic form of appendicitis, and of the causal relationship between this chronic affection and suppurative tumors occurring in the right iliac region, as also of the comparative frequency of occurrence of this condition, and the more acute variety.

The establishment of these points rounds out the first stage in the evolution of knowledge concerning the vermiform appendix.

Primary lesions were definitely recognized as occurring in the little organ by Métier, and this fact should thereafter have greatly modified medical consideration of right iliac disorders.

We now come to one of those curious lapses following a new train of thought with which the history of medicine, indeed, of science, is replete. Perhaps Métier was ahead of his time, for after all surgical treatment as a palliative for appendicitis really could not have advanced far under the then existing conditions, in a period before the work of Lord Lister changed the

whole scheme of things in the field of surgery.

Following Métier's work we find the trend of thought on abdominal diseases dominated by Dupuytren, the accorded greatest surgeon of his time.

Dupuytren preferred to take an exactly opposite view to that advanced by Métier. Didactically he states that the structure of the ileocaecal valve, and the caecum itself, were the factors determining the frequency of right iliac fossa conditions as opposed to those occurring in the left iliac region. The appendix he chooses to discount entirely as an influence in such a determination. His theory held that right iliac suppurative tumours arose from caecal disturbance, and despite many strenuous objections from followers of Métier, it was the prevailing viewpoint for the next 50 years.

Many minor reports of primary lesions encountered in the appendix were placed on record by various observers during this half century, but it remained for the German School of Medicine again to actively bring up the question of lesions of this organ.

A study of the literature during the twenty-five years that the German school held sway seems rather discouraging. Many learned discourses on the subject were printed, but in all of them the writers seemed at a loss to explain the symptoms they so aptly described.

Goldbeck, perhaps the most famous medical writer of this time, describes in 1830 a clinical picture of inflammation of the appendix which is most accurate. He ends, however, by admitting complete failure to interpret the symptoms in question, and this some three years after Métier's admirable hypothesis. Goldbeck invented the unfortunate name perityphlitis, and in so doing succeeded in diverting attention still further from the organ really at fault.

Burne, an Englishman, in 1837 introduced the name tumphlo-enteritis, and despite some really excellent work on

right iliac abnormalities, really hindered progress by this choice piece of meaningless nomenclature.

Hodgkins, a contemporary of Burne, gives some excellent autopsy records of appendix lesions, as do Addison, Bright and Copland, also of the English school. The latter physician discriminates for the first time between inflammation of the appendix, inflammation of the caecum, and inflammation of the pericaecal tissue.

Copland first suggests the possibility of trauma, and physical exertion exciting these conditions.

"Typhlitis," suggested by Albers in 1838, led thought even further astray from the appendix, and Burne's "tumphlo-enteritis" succeeded in almost completely cloaking this organ as being the possible seat of primary lesion in right iliac fossa conditions.

In 1848 Hancock, a London medical man, actually diagnosed a case as inflammation of the appendix before fluctuation appeared, and incising the mass in the iliac fossa relieved it of a quantity of turbid serum, the patient ultimately recovering. In this operation we have the first modern trend in the history of surgery of the appendix.

The beginning of the nineteenth century begins to show an inclining to the earlier views of Métier. By 1873 eight cases of treatment of appendicitis by surgical procedure prior to the appearance of fluctuation, had been recorded, showing the rapid development of such therapeutic measures.

Willard Parker in 1867 made a great stride forward in operative treatment of appendicitis. This New York surgeon was convinced that it was not desirable to wait for fluctuation to appear before making incision. He believed that nature attempted to protect life by walling off the pus collection with adhesions. The possibility of ulceration of the wall of this pocket, with discharge of its contents into the peritoneal cavity, and the grave results attendant on such a happening, he recognized. Operation be-

fore fluctuation would therefore eliminate the possibility of such a rupture, and this measure he adopted as his method of treatment.

Lord Lister's principles of antiseptis, coming into general use at this time, gave a new impetus to abdominal operations.

Resection of the appendix was performed for the first time by Kronlein of Germany in 1884, following a suggestion of such a procedure made by Mikulicy, a professor of Krakow, in the same year. The result was not favourable, the appendix having been found perforated, but the operation was undoubtedly a big step forward in the abdominal surgery of that day.

We now come to the work of Dr. Reginald Fitz of Boston, mentioned at the beginning of this paper.

We must remember before considering his work and its influence on right iliac fossa diseases, that whereas up to this time many operations had been done on the appendix, they were not always understood as remedying lesions arising directly from that organ, and that up to the time of Fitz the actual name of "appendicitis" was never made use of.

The essential point grasped by Fitz was that the various abdominal disorders known as perityphlitis, typhlitis, tymphlo-enteritis, caecites, etc., were really nothing but the different manifestations of morbid processes arising primarily in the vermiform appendix.

He thus swings back the pendulum of thought to the early discriminations of M^étier made fifty-nine years ago in 1827.

Fitz first used the word "appendicitis" and says, "The word was coined by me for practical purposes. I wished to draw attention to inflammation of the vermiform appendix as the pri-

mary lesion, and that to which it was to be directly applied."

The paper of Fitz found the medical profession in an expectant and receptive attitude, and his masterful presentation of the subject easily transferred the condition henceforth to be known as appendicitis from the realm of internal medicine to that of surgery, and wiped out in one stroke much of the earlier misleading nomenclature.

New operative procedures were quickly developed; coeliotomies with removal of the appendix became increasingly common. Investigation turned a very bright spotlight on this little organ, and it was fully appreciated to just what extent it had been responsible for illness and death.

The subsequent history of appendicitis follows more particularly the improvement in operative technique suggested and practised by those following Fitz, and it brings us up to the present day in which simple acute cases of appendicitis, without complications, are attended with little more risk in the hands of a competent surgeon than that arising from a mere phalangeal amputation.

Undoubtedly further developments in this particular operation can only rest with the development of individual technique. Whilst no radical changes can be reasonably looked for, the genius of man will surely do much to smooth down the small imperfections which may be still extant, and a future generation may even consider our procedures a tedious demonstration as compared to the methods of their day.

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SURGICAL TREATMENT OF PARATHYROID TUMORS

By A. M. LARGE, B.A., '36.

The purpose of this paper is to deal briefly with the anatomy and physiology of the parathyroid glands, and to discuss at some greater length the pathological and clinical aspects of parathyroid tumors, and their surgical treatment.

Anatomy.

The parathyroid glands are small brownish red bodies, usually four in number, situated, as a rule, between the posterior border of the lateral lobes of the thyroid gland and its capsule. They present the appearance of flattened oval discs, having average normal dimensions of $6 \times 3\frac{1}{2} \times 1\frac{1}{2}$ mm. The superior pair of the glands occupy a more or less constant position at the level of the lower border of the cricoid cartilage behind the junction of the pharynx and the oesophagus. The inferior pair, although as a rule found at the lower poles of thyroid, may be situated anywhere along the inferior thyroid artery or even in the anterior mediastinum.

A survey of autopsy findings reveals the presence of less than four parathyroid bodies in under one per cent. of bodies and more than four in some 33% of bodies, these latter largely situated between the thyroid gland and the mediastinum.

Microscopically, the gland consists of intercommunicating columns of cells supported by connective tissue, with a rich blood supply of sinusoids. Four types of parenchymatous cells can be distinguished.

The lymphatics drain to those of the thyroid gland or the thymus. Nerve supply is from the sympathetic (a) directly from the superior and middle cervical ganglia and (b) indirectly from the plexus on the posterior lobe of the thyroid.

Physiology.

Within the last few years, it has been conclusively demonstrated by Collip and others that the parathyroid bodies are the main link in the chain concerned with the governing of calcium and phosphorus metabolism throughout the body. This has been made possible chiefly through the isolation of potent parathyroid hormone extracts from the gland by Collip in 1925.

Experimentally (a) removal of the glands results in decreased serum Ca, normally 10 mgm. %, to approximately 5-7 mgm. %, and with it, hyperexcitability of the central and peripheral nervous systems and consequent tetany. (b) injection of excess amounts of the hormone leads to an increased serum Ca to 16-18 mgm. % with hypoeccitability of the nervous system; and if prolonged, to those bony and urinary changes typically seen in full-blown cases of parathyroid tumor.

Pathology.

The most recent and conclusive work in this field has been carried out by a group of pathologists and surgeons working together at the Massachusetts General Hospital, in Boston. From their observations a classification, which fits in with both clinical and pathological findings, has been evolved. It is as follows:—

(a) General enlargement of the parathyroids due to functional hyperplasia but no evidence of hyperparathyroidism—seen in such conditions as rickets, osteomalacia, pregnancy and nephritis.

(b) General enlargement and hyperplasia with hyperparathyroidism.

(c) Focal hyperplasia (adenoma) of one or more parathyroid glands as-

sociated with hyperparathyroidism. In this work an adenoma may be considered as a focal collection of actively functioning gland cells that does not conform grossly or microscopically to the architecture of the normal gland.

(d) Carcinoma.

As functional hyperplasia does not come within the scope of this paper and carcinoma of the parathyroid is conspicuous, in the literature, by its absence, these two groups may be summarily dismissed, and our attention focussed upon the true parathyroid tumors, including diffuse hyperplasia with hyperparathyroidism, and solitary adenomata with hyperparathyroidism, the existence of one of these types precluding the possibility of the presence of the other. The possible occurrence of parathyroid tumors without hyperparathyroidism, having no constitutional effects and being anatomically insignificant as well, need not further concern us.

Now since the outstanding constitutional disturbance in hyperparathyroidism is a rise in the blood serum Ca, from a normal of 10 mgm. % to a level of 13-17 mgm. %, with a coincident lowering of serum P below the normal of 5 mgm. %, and a rise in plasma phosphatase normally 2-4 units to 4-17 units, it might be well at this time to consider the relationship between laboratory and clinical aspects of such conditions, with subsequent reference to the surgical technique employed in the proper treatment of the two types.

Symptomatology and Physical Observations.

It should be pointed out (1) that in these cases the serum Ca is persistently raised, despite low Ca diet (2) that urinary and faecal Ca and P are both high, and (3) that since Ca and P levels of other tissues remain unchanged, this excretion must result from a resorption of the calcium salts of bone. At the same time it will be realized that the urinary tract is put

under considerable strain by the excess calcium excretion so that urinary calculi may form or calcium deposits in the kidney parenchyma may lead to the production of chronic nephritis. Clinically, then, we may consider the signs and symptoms to come under three main headings:

(a) Those due to hypercalcaemia, *per se*;

(b) Those related to skeletal changes;

(c) Those due to increased calcium and phosphorus in the urine.

(a) The main effect of *hypercalcaemia, per se*, both experimentally and clinically, is to produce a decreased excitability of the nerve-muscle apparatus, so that more electricity is required to cause a muscular contraction than in the normal. Thus, in patients, hypotonia with probably flatfoot, lassitude, constipation, anorexia, and general sluggishness and malaise are noted—it is interesting that all these symptoms disappear practically immediately after operative removal of the tumor.

(b) *Skeletal Involvement* varies from no noticeable change to almost complete disappearance of the bones, and death from inability to raise the thorax in respiration. These bony changes appear to occur, in general, in one of two forms (1) Von Recklinghausen's disease of bone also called osteitis fibrosa cystica; which although a rare condition, is known to be caused by over-activity of the parathyroid glands. (2) Osteoporotic form, in which there is general decalcification of the skeleton but no bone tumors or cysts.

In both these conditions, bone pains appear early, especially in the back, and due to bony changes and weakness in the spine, bowing with noticeable decrease in height has often been observed. At the same time a decrease in haemopoietic elements of the bones may lead to secondary anaemia and leucopenia. The x-ray indicates a general, fundamental increased radiability of the skeleton with secondary deformi-

ties, cysts, tumors and fractures, depending on the type of bony involvement.

(c) The *urinary changes* tend to become manifest in cases of severe hyperparathyroidism of short duration with relatively high calcium intake, while the more prolonged and insidious cases are prone to affect the bones. In the urinary cases, polyuria and polydipsia may predominate, renal colic or other manifestations of nephrolithiasis may be the first and only symptom, or again, chronic nephritis with seriously impaired renal function from parenchymatous deposition of calcium may characterize the picture. As a result of their work in Boston, Albright and others believe that serum Ca and P determinations should be performed on every case of urinary calculus, to rule out the possibility of hyperparathyroidism.

Diagnosis.

Those workers who have undertaken the most recent and exhaustive study of this subject point out that by carrying on a series of measurements of the Ca, P and phosphatase of the blood serum on a low Ca diet, hyperparathyroidism can, as a rule, be readily distinguished from all diseases with which it might be confused. It is also shown that single determinations of serum calcium on an uncontrolled diet are of little or no value in diagnosis, and have led to the assumption of erroneous conclusions in many cases. Any case showing persistent serum Ca above 11 mgm. % and serum P below 3.5 mgm. % should be suspected to be suffering from hyperparathyroidism.

Thus the clinical findings, including any or all of the three main types already mentioned, confirmed by these typical laboratory findings, make the diagnosis reasonably certain. For example, in such conditions as senile osteoporosis, Paget's disease of bone, osteomalacia, and fragilitas ossium, the serum Ca is always found to be normal,

or below normal, although some of the clinical aspects may appear identical with those of hyperparathyroidism.

Treatment.

Before proceeding to discuss the therapeutic measures advocated in this condition, I should like to refer to the work of certain surgeons who have undertaken the removal of one or more parathyroid bodies in conditions other than true hyperparathyroidism. Oppel, Leriche, and Ballin working independently have all attempted to relieve certain selected cases of arthritis by parathyroidectomy. This procedure, I believe to be entirely unwarranted, for the following reasons:—

(a) In all these cases, single serum Ca determinations, with no dietary control or metabolic studies, were performed—the existence of true hyperparathyroidism was, therefore, not established.

(b) In a series of some 21 cases of parathyroid tumor in Boston, many of them far advanced, no sign of any type of arthritis was present.

(c) The results claimed by these gentlemen were more than likely due to rest in bed, diet changes in hospital, or spontaneous remission.

(d) When normal parathyroid glands are removed, it has been shown that the glandular tissue remaining undergoes compensatory hypertrophy until the previous level of parathyroid function is established.

Therefore, I believe that treatment of hyperparathyroidism, as such, should be reserved for those cases shown by suitable clinical and laboratory methods to be a true hyperfunction of the parathyroid glands.

Non-surgical treatment of hyperparathyroidism has never proven successful (a) x-ray therapy applied to the glands or bones is valueless—some decrease in bone symptoms may result but fibrosis and anaemia are increased (b) high Ca and P diets stop the de-

calcification but increase the tendency toward urinary symptoms (c) Vitamin D has no effect on the Ca or P balance in this condition.

It then remains only to consider the methods of *surgical treatment* of cases of hyperparathyroidism.

Surgical Pathology.

A tumor palpable on physical examination is unusual, having been noted in only some 15-20% of cases,—this being no doubt due to the fact that parathyroid tumors lie deep in the neck or mediastinum, and the pliant nature of parathyroid tissue enables these bodies to mold themselves to the form of adjacent structures.

At operation, *adenomata* resemble the normal gland in color, often a well-defined capsule is present, the latter sometimes thickened by calcification which tends to conceal the characteristic brown colour which becomes evident only when the gland is sectioned. Large tumors are easily recognized when exposed, but smaller ones are difficult to distinguish from the normal, as considerable variation exists in the size of the normal gland. As well as this, small tumors may be confused with:

- (a) small thyroid nodules
- (b) lymph or haemolymph nodes.
- (c) small collections of fat.

The characteristic shape — flattened oval discs — and the tiny vascular pedicle always present, are the main adjuncts in identification of the parathyroid bodies at operation.

If the picture is that of generalized hyperplasia with hyper-parathyroidism, rather than adenoma, general, flattened, diffuse enlargement is the rule rather than the plump appearance presented by an adenoma.

It must also be remembered that one or more of the four glands usually seen, or sometimes accessory glands, with or without tumor present, may be encountered anywhere between the lower border of the cricoid cartilage

and the superior mediastinum, and anteroposteriorly between the fascia deep to the infrahyoids and the prevertebral fascia respectively.

Operative Surgery.

The importance of finding and removing the tumor in the first surgical exploration cannot be exaggerated, since a search through scar tissue at a secondary operation offers many further obstacles to success.

Meticulous haemostasis is extremely essential through the entire operation in order to avoid staining the tissues and thus obscuring the typical colour of the parathyroid bodies—the smaller vessels encountered should be doubly ligated with fine silk before sectioning. At the same time, exploratory procedure must be carried out most cautiously in order to avoid trauma to the parathyroid glands—as slight injury to the latter will result in the rapid production of a haematoma which will tend to mask the identity of the gland, and at the same time predispose to post-operative tetany. Here should be mentioned the danger of interfering with the blood supply to normal parathyroids as another main factor in the production of tetany after operation. Churchill and his associates are careful to avoid cutting into the thyroid gland with resultant haemorrhage, and use fine silk traction stitches instead of double hooks to retract the thyroid gland—the technique employed being that of neurosurgical procedure rather than that of subtotal thyroidectomy.

After a diagnosis of hyperparathyroidism is reached, special X-ray plates should be made preoperatively, to try to locate the tumor, either by means of its calcified capsule or by displacement of the trachea or oesophagus. Even if the tumor cannot be located by this means, operative procedure is undertaken.

A wide collar incision is made, and the neck and both anterior and posterior mediastina explored by the finger, a substernal tumor being delivered

into the operative field by gentle traction. The location of these mediastinal tumors is facilitated by the constant presence of a vascular pedicle passing down to them from the inferior thyroid artery. Removal of normal parathyroid bodies or interference with their blood supply is absolutely contraindicated even if no tumor is found, since such a procedure gives no benefit, and increases the danger of post-operative tetany in a subsequent operation. If the diagnosis is confirmed and no tumor found, the mediastinum may be explored under direct vision by section of a portion of the manubrium sterni. If still no tumor is found, a lobe of the thyroid can be removed if any evidence of a parathyroid inclusion tumor exists.

When the enlarged gland, glands or tumor are found, it must be decided how much parathyroid tissue is to be removed—an adenoma is usually solitary and should be removed together with the parathyroid body in which it is found.

Subtotal parathyroidectomy is indicated in a goodly percentage of cases of hyperparathyroidism, as follows:

(1) Where normal parathyroids have been removed or their integrity damaged at a previous operation.

(2) In cases of large single adenomata of long standing with evidence of depleted Ca and P reserves, that is, decalcification, since the hungry bones taking up as much Ca and P from the blood as possible after operation, are more than likely to precipitate tetany.

(3) In cases of generalized hyperplasia with hyperparathyroidism, subtotal resection is certainly indicated. Here conservative treatment is the wisest course since post-operative tetany in these cases is frequent and difficult to treat. At the same time the residual tissue with its blood supply should be placed in an easily approachable position in case a secondary operation is subsequently found to be necessary.

Results of Operation.

The most striking feature is an immediate correction of Ca and P metabolism with the assumption of normal Ca and P levels in the serum, thus confirming and being the final step in diagnosis and efficacy of treatment. The serum Ca falls with dramatic rapidity, and tetany usually occurs, may be prolonged, and may appear with serum Ca normal or above normal, when hypercalcaemia has been present for a long time. This tetany is controlled by a high Ca diet, the administration of calcium gluconate, irradiated ergosterol, and parathormone, since after a few days the constitution becomes accustomed to the new level of serum Ca and the tetany tends to disappear spontaneously.

Improvement in the symptoms of hyperparathyroidism results within a few days; muscle and bone pains, malaise, sluggishness and etc., are promptly relieved, the patient often stating that he feels better than he can remember for many years. But many months must pass before bone changes are demonstrable in the X-ray; bone tumors may disappear, but the bone cysts apparently persist. Renal function may improve to an extent as yet unknown, and it is reasonable to assume that recurring nephrolithiasis is eliminated.

Prognosis is extremely good, provided the diagnosis is made sufficiently early, that is, while the patient is still in fit condition to undergo the trials of a prolonged surgical operation, and provided that the procedure is carried out by a surgeon well acquainted with the technique and difficulties of such a complicated dissection.

Summary.

Parathyroid tumors with hyperparathyroidism are of two types: (a) generalized enlargement and hyperplasia of all the glands; (b) solitary adenoma of one, rarely of two, of the glands.

Both of these types although presenting numerous pitfalls in operative technique, yet yield most gratifying clinical results in the hands of skilled surgeons working in collaboration with diagnosticians of the proper calibre.

Parathyroid tumors to-day are not of interest to the average medical prac-

titioner, due to the infrequency of their occurrence or perhaps of diagnosis, but with a fairly definitely established relationship between nephrolithiasis and parathyroid hyperfunction it would certainly not be surprising to see interesting and practical developments in this field in the near future.

ESSAY "ON THE TEACHING OF ANATOMY"

A. Y. MACKINNON, '38.

If Hippocrates were to step into one of our modern anatomical laboratories, he would find there a strikingly different method of teaching anatomy from that which obtained in his day. The coldly scientific dissections performed in well-lighted rooms, the finely tempered instruments wielded by white-gowned students, would contrast sharply with his philosophic discourses on the innate heat of the heart, or a like subject, each point being eloquently argued by those bearded disciples that frequented the olive groves of old Athens throughout the long, sultry afternoons. He would find us less superstitious but perhaps too phlegmatic; we would seem more exact perhaps though less logical. Our present state, however, desirable or undesirable, it seems, is not the result of any sudden enlightenment, but rather the essence and distillate of the countless ages in which man has striven to learn the mysteries of his human frame.

As Pleistocene period gives way to recent, primitive medicine men, half priest, half witch-doctor, instruct their disciples in the casting of spells and curses, propitious phases of the moon, the despatching of devils and such.

The Assyrians, Babylonians, and Egyptians had their physicians, and there is evidence that the people of Thebes in Upper Egypt understood sufficient anatomy to perform simple operations as early as 1,000 B.C. However, for the first scientific dissection on record we must turn to the Greek Alcmeon who dissected the animal and

human body in the year 500 B.C. in the colony at Croton in Southern Italy. Down to the days of Hippocrates, however, we have only occasional records of such serious work being done, although a certain Carystus wrote a treatise on Anatomy which has since disappeared. The Hippocratic collection contains one book on Anatomy, which unfortunately is quite corrupt due to repeated notation and translation by scholars of the late Athenian and early Alexandrian school. The chapter on Fractures and Dislocations, however, is one of the best and shows a real knowledge of the anatomy of the shoulder-joint.

Passing on to Aristotle and the Peripatetic school we find the body studied under the four humours and it continued to be studied in this manner up to the time of Vesalius. Although Anatomy was still taught in the philosophic schools of Greece, the centre of the stage of culture after Aristotle's death is occupied by Alexandria, founded by Alexander Magnus, patronized by the Ptolemaic line and lead in thought by the illustrious pair, Herophilus and Erasistratus. Here dissections were performed, lectures delivered on Anatomy, and treatises written. The immense library of half a million volumes was well stocked with anatomical literature. Here we have the first record of a woman studying the healing art, a certain Agnodice. But it is hard to separate legend from fact and she may never have existed. Although the name of Alexandria is linked with

vivisection, we are inclined to doubt that it was practised. The popular antagonism to dissection probably gave rise to these spurious reports.

Slowly Alexandria declined under the rise of Rome, and after the destruction of her library by the Persians in 640 A.D. (the manuscripts served the baths as fuel for six months) she became unimportant. It was at Rome that the first medical schools were founded in the year 60 B.C. The school consisted originally of a band of physicians who took their apprentices about with them on their rounds, the instruction being largely clinical. Feeling a need for centralization the groups built meeting-places and arranged instruction in medical subjects, including Anatomy. Under Vespasian these schools flourished, the buildings were enlarged, and the salaries of the instructors paid by the state. In this period before Galen, we have a general decadence, attendant on the slow disintegration of Rome, the rise of Christianity, the Graeco-Roman respect for the dead and the common repugnance for the dissector. It is probably for this latter reason that the great Pliny scores Anatomy. Dissections of animals became reduced to votive offering and mere entrail-observing, similar to the Babylonian divinations with sheep's liver.

Galen's knowledge was the product of four teachers, all leaders of thought at that time. Combined with this knowledge was a very successful philosophy of life. At the age of fifteen he was taken by his father to lectures on philosophy, later studying at Pergamum under Satyrus and at Alexandria. He had a distinct flair for writing and began to cultivate it while still a boy. After Marinus, Satyrus, Pelops and Numisianus could teach him no more, he set out to study Anatomy on his own. He dissected to prove his position: that the human body was flawlessly designed, each part serving its function to perfection. Thus he stressed the beautiful mechanisms of the

joints, the ultimate nicety of form interrelated to function. He attracted no disciples, left no school, but his influence on Medicine is still felt. Galen, however, preceded the deluge. The mists of ignorance and superstition clouded the outlook of Europe for nearly a thousand years, during which time all culture went by default and precious manuscripts were destroyed.

In the near East culture still flourished, however. From the eighth to the thirteenth centuries the Arabs practised Medicine and the great Avicenna laid down his canons of treatment. The Latin and Greek originals were translated to Arabic and new texts drawn up. Thus when Europe, roused from its lethargy, it turned to Arabic writings for the wisdom of the Ancients. The scholasticism present in the mediaeval monasteries was a good thing. The retranslation of Persian and Arabic copies stimulated the study of the classics direct. In this new movement the Universities were born, some being established in the thirteenth century. The Medical faculties formed were unimportant, being scholastic. Dissections, however, were revived with accompanying progress, the first one on record being performed in 1300 A.D. It is interesting to note that the faculty of medicine at this early period was subordinate to the Faculty of Law. Those were early days! The dissections were in the nature of an inquest or post-mortem, a physician doing the actual work. Thus the procedure was more in the nature of a verification of Avicenna than an anatomical research. One of the earliest illustrations in this connection was a post mortem scene and was included in the Anatomy for interest rather than instruction. Gradually as books became numerous, pictures of parts were included, crude at first, then more accurate until we get the beautiful plates of Vesalius and Fallopius, Canano, Benedetti, Carpi and Albrecht Durer. At this time charts and diagrams became popular and Henri de Mondeville of Bologna intro-

duced them at Montpellier, though Sylvius at Paris scorned their use.

Across the Channel, however, there is no record of the teaching of Anatomy as such before the sixteenth century, though it was taught, of course, under Surgery and Medicine. The difficulty in procuring material for dissection was lessened by legislation permitting anatomies to be made at the Barber-Surgeons Hall and by giving dissection rights and awarding fellowships to the University of Cambridge. The College of Physicians were granted as many bodies as they needed, in return for which each member was obliged to deliver a lecture on Anatomy. The subjects generally used were felons, convicted murderers and so forth. This worked out so well that soon a law was passed permitting the dissection of all murderers, the point being to train more surgeons for the army and navy, and incidentally discouraging outlawry.

Outside of the Universities and the Company of Barber Surgeons and the College of Physicians, instruction was given by surgeons to those who could afford it. These lectures were delivered generally in taverns and coffee-houses where the wealthy and educated were to be found. Private courses in Anatomy were advertised in the press and delivered two or three times a year, the course taking about six weeks to give, with two or three lectures a week. The cost varied with the extent, ranging from three to five guineas a course and the matters dealt with were guaranteed not to offend the gentlemen attending. The time at which the lectures were delivered was generally five or six o'clock, but William Hunter changed the hour to two p.m. because the pupils of that day could not resist the spell cast by David Garrick who was then at his zenith.

In view of the difficulty in obtaining sufficient human material, charts, models, and casts appeared, these all being viewed with scorn by Hunter. In Great Britain and on the Continent an-

atomies were published bearing woodcuts and engravings of parts. This matter of illustration is a very vital one in the history of teaching anatomy. The beautiful plates of Vesalius, the more accurate, if less beautiful figures by Estienne, Leonardo's drawings, all these have been of untold value in the education of the student. It is one thing to write whole chapters on the complexions and the definitions of organs, the source of innate heat, the seat of the emotions, the production of vital spirit, the moisture of the brain; it is another matter to draw them. Thus illustrations have ridded Anatomy of much of the vagueness and ambiguity that arises in written description. One of the strongest selling points of the early editions of Gray's Anatomy was the admirable engravings from the pen of that excellent draughtsman, Dr. H. V. Carter. Similarly the splendid pictures in the current atlases and texts elucidate many of the finer points for the modern students.

One cannot deny, however, the genuine inspiration derived from the lecture of a worthy professor. If Vesalius will be honored as the founder of modern anatomy, then Gunther will always be revered as a teacher loved by all his pupils. As in all things the actual manner of imparting knowledge changes with the years. At some periods, as in the Egyptian and Roman, it was almost entirely clinical. The Hippocratic and Peripatetic schools resembled the present-day seminar or discussion group. In early monastic times it was a scholasticism. The Universities of the Middle Ages employed a three person system: a professor who, sitting in an elevated chair or cathedra, would read excerpts from the classic writers, Galen, Hippocrates, Avicenna. The demonstrator or ostensor, would then point out on the cadaver the parts described and the incisions necessary to display them, the actual dissection was left to a menial. This system obtained for many centuries and is still practised in theory to-day.

